A systematic review of vertical transmission and antibodies against SARS-CoV-2 among infants born to mothers with COVID-19

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Abstract

Amidst the Coronavirus Disease 2019 (COVID-19) pandemic, evidence on vertical transmission and natural passive immunity among the newborns exposed to COVID-19 is scanty and varies. This pose a challenge on preventive interventions for the newborns. We conducted a systematic review to first, determine the likelihood of vertical transmission among COVID-19 exposed infants and second, determine whether antibodies against Severe Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)/ COVID-19 virus exist among COVID-19 vertically exposed but negative infants. This review registered in PROSPERO searched evidence from PubMed/ MEDLINE and Google Scholar, among others. About 517 studies were retrieved, where only 33 articles (5.8%) qualified for final analysis. A total of 205 infants born to SARS-CoV-2 positive mothers were pooled from 33 eligible studies. Overall, 6.3% (13/205; 95%CI: 3.0%-9.7%) of the infants tested positive for COVID-19 virus at birth. Of 33 eligible studies, 6 studies (18.8%) reported about IgG/IgM against SARS-CoV-2. Anti-SARS-CoV-2 IgG/IgM were detected in 90% (10/11; 95%CI: 73.9%-107.9%) of infants who had no COVID-19 but vertically exposed. In conclusion, the current evidence revealed a low possibility of vertical transmission of COVID-19 while antibodies against SARS-CoV-2 were detected in most of the infants who had no COVID-19. Further studies on perinatal outcomes and the magnitude of natural passive immunity in infants born to mothers with COVID-19 are warranted.

Introduction

Coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)/ COVID-19 virus was first reported from Wuhan, China in late December 2019[1]. Since then, there has been a rapid increase in the number of new cases and deaths from the disease, and overall changing in the disease landscape[2]. In its 121 situation report on May 20, 2020, the World Health Organization (WHO) confirmed a total of 4,789,205, COVID-19 virus positive cases, 1,980,118 recoveries, and 318 789 deaths[3].

Like other infectious diseases, pregnant women continue to be vulnerable to COVID-19[4]. Literature has reported the possible potential implications of COVID-19 in pregnancy but the debate on a possible vertical transmission is still ongoing[4,5]. Few studies have associated the potential influence of COVID-19 infection from an infected pregnant woman to her fetus or newborn, these include the possibility of miscarriages, preterm delivery and neonatal infections[6,7]. The previous epidemic from Severe Acute Respiratory Syndrome Coronavirus 1 (SARS-CoV) reported no prenatal transmission of SARS. This was confirmed through testing of amniotic fluid and umbilical cord blood obtained during cesarean section together with throat swab of the newborn[8,9]. Evidence have started to show the likelihood of mother to child transmission of COVID-19 infection among the confirmed neonatal infections[10–12].

On the other hand, the detection of immunoglobulin (IgM/IgG) against SARS-CoV-2 IgG and IgM among infants born COVID-19 confirmed mothers but themselves tested COVID-19 negative have been reported[13–18]. This serological evidence raises more concern about the possible mother to child transmission of

antibodies against SARS-CoV-2[8,9]. Evidence seems to be scant and varying with regards to both vertical transmission and antibodies against COVID-19 virus among the exposed newborns. To address this scientific gap of clinical and policy implication, we conducted this systematic review to first, pull evidence to examine the likelihood of vertical transmission and antibodies against SARS-CoV-2 among newborns exposed to COVID-19.

Methods

Design: This systematic review was conducted to address the following question, "Is there a vertical transmission and antibody responses against SARS-CoV-2 in infants born to mothers with COVID-19?". A systematic review protocol was developed following Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines[19] and registered in the International Prospective Register of Systematic Reviews (https://www.crd.york.ac.uk/prospero/: PROSPERO database registration number: CRD42020185362)

Search strategy: Articles were retrieved using online search engines and library sources, including PubMed/MEDLINE and Google Scholar. Additionally, websites of key healthcare organizations such as WHO and centre for disease prevention and control (CDC) were also searched. Similarly, a grey literature search was done with the help of Google. Data from December 1, 2019 to May 18, 2020 conducted in human beings, and published in English language were included. The strategy was developed for PubMed/MEDLINE (Additional file 1) using keywords and MeSH (MEDLINE) then adapted to other databases. To be as inclusive as possible, the search strategy included the terms covering the concept of immunity and infection among infants born to mothers with COVID-19. Keywords such as vertical transmission, antibody, immunoglobulin, pregnant mother, pregnancy, child, infant, new-born, SARS-CoV-2 and COVID-19 were used.

Eligibility criteria and study selection: To exclude irrelevant studies, two reviewers (GMB and BJN) independently screened the titles and abstracts, and a full-text articles were assessed for further consideration for inclusion. Disagreements on study eligibility were resolved by consensus, and/or a third reviewer was consulted if necessary. If the information on eligibility was unavailable and/ or unclear, study authors were contacted to clarify. The selected studies were included based on laboratory-confirmed COVID-19 infection using quantitative real-time reverse transcription polymerase chain reaction (qRT-PCR) or dual fluorescence PCR and immunoassay such as enzyme linked immunosorbent assay (ELISA) and flow cytometry for antibodies detection, patient pregnant on admission, infant's COVID-19 status soon after birth and infection control and prevention (IPC) measures during and after delivery, i.e., mother wore N-95 during delivery, personnel protective equipment wore by health care workers, infants immediately separated with her mother to a negative pressure room and infants did not breastfeed before samples were taken. This review included, letter to the editor, correspondence, editorial, research article (case report, case series, cross-sectional, clinical trial, cohort, case control study) etc., however, articles that reported on the secondary data such as review were excluded.

Data management: All article citations retrieved from database searches were exported into EndNote software version X7 (Thomson Reuters, 2015) where duplicates were identified and removed. Identified publication(s) were analyzed using criteria based on vertical transmission and/ or IgG/ IgM against SARS-CoV-2 and maximum correspondence with inclusion criteria (Fig. 1).

Data extraction and quality assessment: The reviewers independently extracted the variables of interest from the selected studies using data extraction. Data extraction form was developed in Excel spreadsheet 2010 (Microsoft Corporation, Redmond, WA), pre-tested on 3 eligible articles and adjusted accordingly (Table 1). The primary endpoints were birth outcomes, such as COVID-19 infection, IgM and IgG against SARS-CoV-2. PRISMA-P guideline[19] recommends a quality assessment of the included literature, but given the time from the first report of COVID-19 (December 31, 2019), most of the extracted studies were case reports with a very small number of participants (mostly one participant) per study. In this case, authors decided not to perform the risk assessment as described elsewhere[20], heterogeneity and meta-analysis

Summary measures and synthesis of results: A summary estimate of proportions for COVID-19 virus positive and IgG/IgM against SARS-CoV-2 among infants born to mothers with COVID-19 were determined using Open Meta Analyst software[21].The statistical measures included along with 95% confidence interval (95%CI) for continuous variables. The narrative was written by the lead reviewer (GMB) and then checked independently by two reviewers (BJN and DLM). The variables that were missing from included articles were recorded as not reported. No statistical test was applied in handling missing data. However, available information was used in recalculating some variables using the Open Meta Analyst calculator.

Results

Characteristics of the studies included

A total of 517 studies were pooled from a systematic search, where only 33 articles (5.8%) were eligible for final analysis. Of 33 included studies, 21 were case reports (65.6%), 10 retrospective studies (28.1%) and 2 (6.3%) prospective studies. From 33 articles, a total of 205 infants were born to COVID-19 virus positive mothers. All articles reported on COVID-19 transmission, but only 6 studies (18.8%) reported about IgG/IgM against SARS-CoV-2 among infants born to COVID-19 virus positive mothers. Most of the studies, 19 (59.4%) were conducted in China. Twenty-three studies (71.9%), reported that mothers delivered through cesarean route with preterm delivery in the majority of the studies, 20 (62.5%). Infection prevention and control (IPC) during and after delivery was reported to be in place by the majority of the included studies, 21 (63.6%) (Table 1).

The proportions of possible vertical transmission of COVID-19

Thirty studies were analyzed to determine the possible vertical transmission of among infants born to COVID-19 virus positive mothers. A total of 205 infants were born to COVID-19 virus positive mothers, where only 6.3% (13/205; 95%CI: 3.0%-9.7%) of the infants tested positive for COVID-19 virus at birth. Of 33 included studies, 21 were case reports (65.6%), 10 retrospective studies (28.1%) and 2 (6.3%) prospective

studies. The proportions of the infants who contracted COVID-19 vertically from their mother were 22.2% (6/27; 95%CI: 6.5%-37.9%), 2.1% (3/141; 95%CI: -0.3%-4.5%), 7.5% (3/40; 95%CI: -0.7%-15.7%) for case reports, retrospective and prospective study, respectively.

A total of 19 studies (59.4%) were reported to be conducted in China and the remained from the rest part of the world. China reported 4.2% of infants vertically contracted COVID-19 from their mothers (7/167; 95%CI: 1.2%-7.2%) where those who were reported outside China was 10.5 % (6/57; 2.6%-18.5%). Twenty-three studies (71.9%) reported about mothers who delivered through cesarean while 6 (18.7%) studies were vaginal delivery route. The remained studies did not report about the mode of delivery. Cesarean mode of delivery found 10% positive infants (7/70: 95%CI: 3.0%-17.0%) while for vaginal delivery route was 10.3% (3/29; -0.7%-21.4%).

Twenty-one studies (63.6%) reported IPC were in place, other studies IPC were difficult to assess since they were retrospective study with no clear mention of IPC in place, hence assigned not applicable (NA) except two studies where IPC was not reported (NR). In the rest of the studies IPC were not clearly reported. For those with IPC measures in place, 12.3% (9/73; 95%CI: 4.8%-19.9%) of the infants were vertically infected. A total of 20 studies (62.5%) reported preterm delivery while 12 (37.5%) were full term delivery. Two studies gestation period was not reported. In the group of full term, 3.2% (4/124; 95%CI: 0.1%-6.3%) infants tested COVID-19 virus positive while for preterm, 18.4% (7/38; 95%CI: 6.1%-30.7%) of infants born to COVID-19 virus positive mothers were positive.

IgG/ IgM against SARS-CoV-2 among infants born to COVID-19 mothers

Of 33 included studies, only 6 studies (18.8%) reported about IgG/IgM against SARS-CoV-2 among infants born to COVID-19 virus positive mothers. Antibodies were quantified in 11 infants, where 10 out of 11 infants (90.9%; 95%CI: 73.9%-107.9%) had IgG/IgM against SARS-CoV-2. Among 10 infants with detected antibodies against SARS-CoV-2, only one infant (10%; -8.6%-28.6%) tested COVID-19 virus positive. Furthermore, one infant whose antibodies against SARS-CoV-2 were not detected tested positive for COVID-19.

Discussion

This review summarizes the findings from 205 born to mothers with COVID-19. The review aimed to determine the possible vertical transmission of COVID-19 and characterize the immunological feature of infants born to COVID-19 mothers. It was found that, 6.3% of infants born to COVID-19 mothers were infected. The transmission was reported both in preterm[13,22–25] and full-term born infants[23,26] and even where the infection prevention and control measures were in place[13,22,25]. Furthermore, the vertical transmission was reported regardless of the mode of delivery, vaginal[22,27] or cesarean route[13,23–26].

Based on negative samples from amniotic fluid, cord blood, vaginal discharge, neonatal throat swabs or breastmilk, WHO reported no evidence on mother-to-child transmission when infection manifests in the third trimester [28]. However, the recent case report conducted in France, reported the case of transplacental

transmission of a male neonate who was delivered through cesarean section with a gestational age of 35^{+5} weeks. A baby was delivered under a well infection prevention and control settings, amniotic fluid, blood and non-bronchoscopic, nasopharyngeal, rectal swabs, bronchoalveolar lavage fluid samples were collected for RT-PCR and all were positive for the E and S genes of SARS-CoV-2[25].

Findings from the current review were contrary to those reported by Gatta and colleagues[7], from their review which involved 51 pregnant women, where 3 pregnancies were ongoing, among 48 remained pregnancies, 46 gave birth by cesarean delivery and 2 gave birth vaginally, there was no evidence of vertical transmission recorded in all reported births. In this study, all studies were retrospective and conducted in the same country, China. In the current study about 40% of the reported cases were reported outside China. However, the study reported a high number of preterm birth and cesarean delivery route similar to the findings of the current review where 71.9% were delivered by cesarean route and 62.5% by preterm birth. Another rapid review conducted in 32 pregnant women affected with COVID-19 found no evidence of vertical transmission, the study reported 27 cesarean section, 2 vaginal delivery and 47% delivered preterm[6]. A small sample size (n = 32) used in this rapid review may have contributed to the differences in detecting the number of infected infants compared to the current review (n = 205).

On the other hand, this review has revealed evidence for antibodies (IgG/IgM) against SARS-CoV-2 among infants tested negative for COVID-19 but born to COVID-19 mothers. Antibodies were quantified in 11 infants[13–18], where 10 out of 11 infants (90.9%) had IgG/IgM against SARS-CoV-2. One infants whose antibodies were not detected tested positive for COVID-19[13]. In this study[13], negative serology was found both in mother and neonate on the day of birth, and later seroconversion of the mother occurred. The delayed serological conversion curve can be explained in the studies conducted elsewhere in which IgM seroconverts after day 5 from symptom onset[29]. In the study by Zeng et al.,[16], three infants were reported to have elevated IgG levels but normal IgM levels. However, virus-specific IgG/IgM was detected in all six neonatal blood sera samples. The IgG concentrations were elevated in 5 infants. IgG elevation is explained by the fact that, IgG is passively transferred across the placenta from mother to fetus at the beginning of 20^{th} gestational week and become more elevated at the time of birth[30]. But, IgM, which was detected in 2 infants[16], is unlikely to be transferred from mother to fetus due to large molecular structure[31]. The presence of this specific antibody IgG/IgM for the infants who tested negative, and were born to mothers with COVID-19 indicated the possibility of transplacental immunity (natural passive immunity) while the one who had COVID-19 developed antibodies against SARS-CoV-2 following an exposure to virus (natural active immunity).

This study is limited by the small number of participants obtained from the extracted studies, type of the study (low quality study designs, i.e., retrospective studies) included and limited samples from amniotic fluid and cord blood. Nevertheless, this is the first review with more than 200 infants born to mothers with COVID-19. Findings from this review are important for understanding the transmission likelihood and immunological characteristics of infants whose mothers are infected with SARS-CoV-2. In conclusion, currently, there is evidence of a low vertical transmission among infants born to COVID-19 virus positive mothers. Additionally, antibodies against SARS-CoV-2 were detected in most of the infants who tested

COVID-19 negative. Further studies on perinatal outcomes in newborns who vertically acquired COVID-19 and the magnitude of natural passive immunity are recommended.

Declarations

Ethics approval and consent to participate. Not applicable

Data availability. A datasets used and/or analyzed in this review are provided in the main manuscript and its supplementary material (Additional file 1).

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Competing interests. The authors declare that they have no competing interests.

Authors' contributions. GMB designed the study protocol, conducted data extraction and synthesis and drafted the narrative synthesis. BJN designed the study protocol, conducted data extraction and synthesis. DS: designed the protocol and performed data search. DLM revised the narrative synthesis. BFS participated in protocol development and revised the narrative synthesis. All authors have read and approved the final version of this manuscript.

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Table 1

Table 1: Characteristics of the included studies

Author	Country	Design	Mode of delivery	IPC during delivery	Gestation period	Covid19 (positive cases/ total)	IgM/IgG for SARS-CoV-2 (detected/total)
Al-kuraishy et al.,2020[32]	Iraq	CR	Vaginal	In place	Preterm	0/1.0	NR
Alzamora et al.,2020[13]	Peru	CR	Cesarean	In place	Preterm	1.0/1.0	0/1.0
Baud et al.,2020[22]	Switzerland	CR	Vaginal	In place	Preterm	1.0/1.0	NR
Buonsenso et al.,2020[14]	Italy	CR	Cesarean	In place	Full term	0/1.0	1.0/1.0
	Italy	CR	Cesarean	In place	Preterm	0/1.0	NR
Chen et al.,2020[23]	China	CR	Cesarean	In place	Full term	0/3.0	NR
De Socio et al.,2020[15]	Italy	CR	Vaginal	In place	Full term	0/1.0	1.0/1.0
Díaz et al.,2020[33]	Spain	CR	Cesarean	NR	Full term	0/1.0	NR
Fan et al.,2020[34]	China	CR	Cesarean	In place	Full term	0/1.0	NR
	China	CR	Cesarean	In place	Preterm	0/1.0	NR
Lee et al.,2020[18]	Korea	CR	Cesarean	In place	Full term	0/1.0	NR
Li al.,2020[35]	China	CR	Cesarean	In place	Preterm	0/1/0	NR
Liu et al.,2020[36]	China	RT	NA	In place	Full term	0/10	NR
Ferrazzi et al.,2020[27]	Italy	RT	Vaginal	NA	NA	2.0/24	NR
	Italy	RT	Cesarean	NA	NA	0/18	NR
Lowe et al.,2020[37]	Australia	CR	Vaginal	In place	Full term	0/1.0	NR
Lu al.,2020[38]	China	CR	Cesarean	In place	Full term	0/1.0	NR
Lyra et al.,2020[39]	Portugal	CR	Cesarean	In place	Full term	0/1/0	NR
Zhu et al.,2020[40]	China	RT	NA	NA	Full term,	0/4	NR
	China	RT	NA	NA	Preterm	0/6	NR
Zeng et al.,2020[41]	China	PR	NA	In place	Full term	2.0/29	NR
	China	PR	NA	In place	Preterm	1/4.0	NR
Zeng et al.,2020[16]	China	RT	Cesarean	In place	Full term	0/6	6.0/6.0
Zamaniyan et al.,2020[24]	Iran	CR	Cesarean	In place	Preterm	1/1.0	NR
Yu et al.,2020[42]	China	RT	Cesarean	NA	Full term	1/3.0	NR
Yin et al.,2020[43]	China	RT	NA	NA	Full term	0/12	NR
	China	RT	NA	NA	Preterm	0/5	NR

Yang et al.,2020[44]	China	PR	Cesarean	NA	Full term	0/3	NR
	China	PR	Cesarean	NA	Preterm	0/4	NR
Yan et al.,2020[45]	China	RT	Cesarean	NA	Full term	0/4	NR
	China	RT	Cesarean	NA	Preterm	0/1	NR
Xiong et al.,2020[17]	China	CR	Vaginal	NR	Full term	0/1	0/1
Wang et al.,2020[46]	China	CR	Cesarean	In place	Preterm	0/1	NR
Wang et al.,2020[47]	China	CR	Cesarean	In place	Preterm	1/1.0	NR
Sun et al.,2020[26]	China	CR	Cesarean	In place	Full term	1/1.0	NR
	china	CR	Cesarean	In place	Preterm	1/2.0	NR
Sun et al.,2020[48]	China	RT	NR	NA	Full term	0/13	NR
Qiancheng et al.,2020[49]	China	RT	NR	NA	Full term	0/22	NR
	China	RT	NR	NA	Preterm	0/1.0	NR
Peng et al.,2020[50]	China	CR	Cesarean	In place	preterm	0/1	NR
Chen et al.,2020[51]	China	RT	Cesarean	NA	Full term	0/5	NR
	China	RT	Cesarean	NA	Preterm	0/4	NR
Dong et al.,2020[52]	China	CR	Cesarean	In place	Preterm	0/1	1/1
Vivant et al.,2020[25]	France	CR	Cesarean	In place	Preterm	1/1	NR
Note: CR: Case report, PR: Prospective, RT: Retrospective, NR: Not reported, NA: Not applicable, Babies born before 37 weeks were termed as “preterm”							

Additional File

Additional file 1: PubMed/MEDLINE search results

Figures

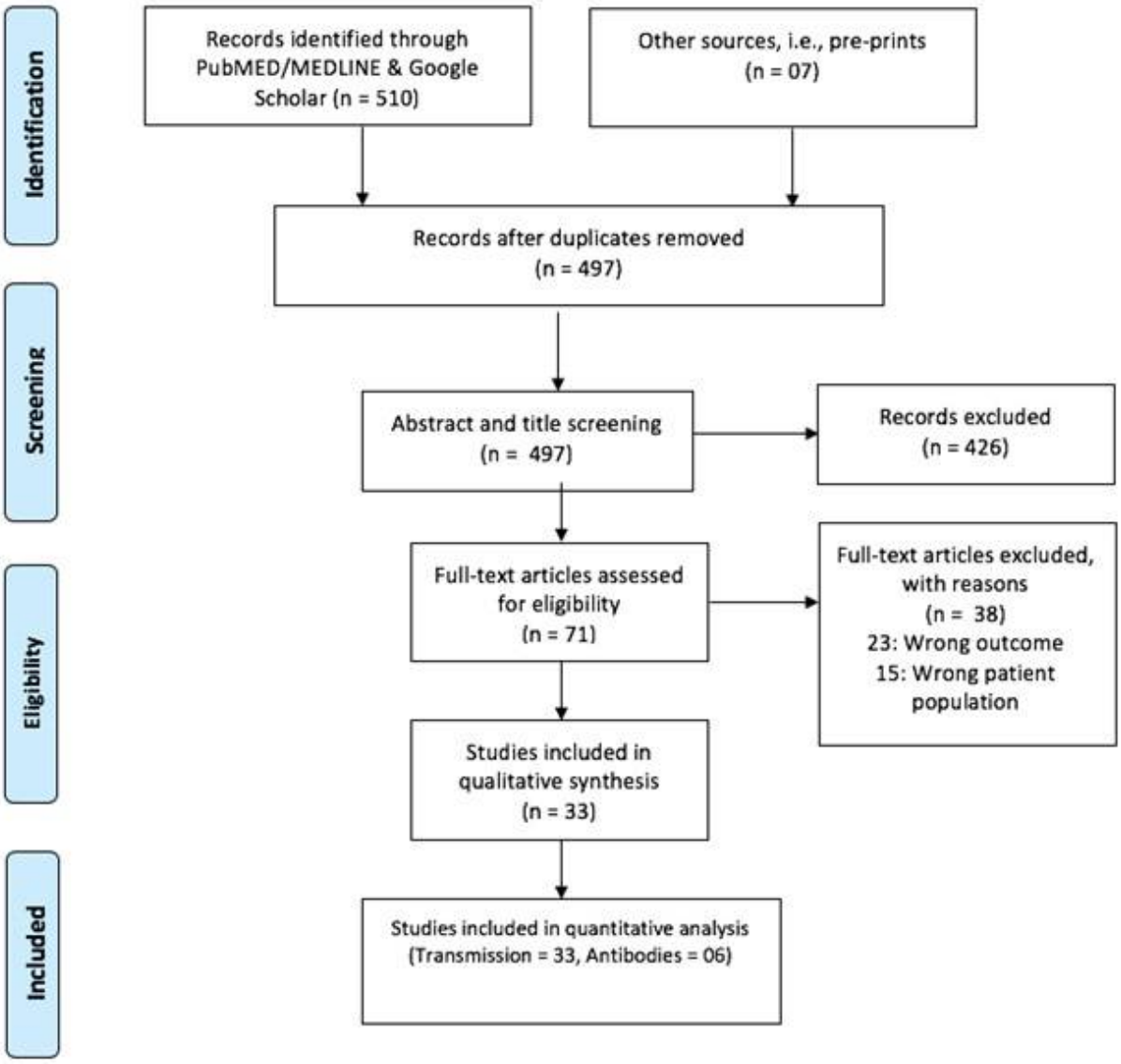

Figure 1

Prisma diagram showing flow of article search and screening

Supplementary Files

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